Remarks

Claims 1, 3-8 and 10-20 are pending. Claims 16-20 are withdrawn by the Examiner. Claims 1-15 were examined and rejected.

Without any intention to acquiesce to the correctness of any rejection or objection set forth in this Office Action and solely to expedite prosecution, claims 1, 6 and 10 are amended to incorporate the subject matter of now cancelled claims 2 and 9. Claim 3 is amended for clarity. No new matter is added.

As set forth above, several paragraphs of Examples 10 and 11 of the specification been amended to recite MAGI1 *domain 2*, as opposed to MAGI1 *domain 1*. This is a typographical error caused by a change in PDZ domain nomenclature during the drafting of the application. One of skill in the art would recognize this as a typographical error because Example 4 (starting on page 95) describes in great detail the construction of the vector used to produce the MAGI1 GST fusion protein used in Examples 11 and 12. In Example 4, the sequences used to produce the MAGI1-GST fusion protein employed in Examples 10 and 11 are called MAGI1 domain 2 (see, e.g., page 197 line 12, the fourth cell of the "description" column of Table 6 on page 97 and page 99 line 5). Accordingly, the Applicants submit that the amendments are supported. Entry of these amendments is respectfully requested.

Request for Interview

The Applicant respectfully requests a telephonic interview with Examiner Lucas *prior to* the mailing of the next Office Action, if any rejections remain after consideration of the arguments set forth below. The Applicant's representative James Keddie can be reached at (650) 833 7723.

Priority

The Examiner is thanked for alerting the Applicants to a potential discrepancy in the Applicants priority claim.

The priority claim of the present application has been amended via a supplemental Applicant Data Sheet (ADS) that accompanies this response. As set forth above, the cross-

referencing paragraph on page 1 of the present application has been amended to conform with the supplemental ADS.

Specification

The specification is objected to for failing to provide antecedent support for claim 3, reciting E6 proteins from HPV strains 16, 18 and 45.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, the paragraph starting on line 1 of page 7 is amended to recite E6 proteins from HPV strains 16, 18 and 45. Support for this amendment is found in claim 3, as originally filed.

In view of the foregoing, the Applicants submit that claim 3 finds antecedent support in the instant specification and, as such, this objection may be withdrawn.

Claim objections

Claims 1, 7 and 10 are objected to for reciting the term "HPV" without first identifying the virus by its complete name.

Without any intention to acquiesce to this rejection and solely to expedite prosecution, claims 1, 7 and 10 are amended to recite "human papilloma virus (HPV)", as suggested by the Examiner.

In view of the above, the Applicants respectfully request withdrawal of this objection.

Claim 3 is objected to for reciting the phrase "16, 18 and 45" rather than "16, 18, and 45", as suggested by the Examiner.

Without any intention to acquiesce to this rejection and solely to expedite prosecution, claims 3 is amended to recite "16, 18, and 45", as suggested by the Examiner.

In view of the above, the Applicants respectfully request withdrawal of this objection.

Claim rejections under 35 U.S.C. § 112, first paragraph - enablement

Claims 1 and 3-15 are rejected for failing to meet the enablement requirement of 35 U.S.C. § 112, first paragraph. In making this rejection, the Examiner indicates that methods

involving a PDZ domain polypeptide comprising the amino acid sequence of Magi-I PDZ domain 2 are enabled.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claims 1, 6 and 10 are amended to recite the subject matter of claim 2, i.e. PDZ domain polypeptide comprising the amino acid sequence of Magi-I PDZ domain 2.

In view of the foregoing discussion, the Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph – written description

Claims 1, 3-8 and 10-15 are rejected for failing to meet the written description requirement of 35 U.S.C. §112, first paragraph.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claims 1, 6 and 10 are amended to recite the subject matter of claim 2, i.e. PDZ domain polypeptide comprising the amino acid sequence of Magi-I PDZ domain 2.

Since claim 2 is not included in this rejection and all claims now recite the subject matter of claim 2, this rejection may be withdrawn. Withdrawal of this rejection is respectfully requested.

Claim 3 is rejected for failing to meet the written description requirement of 35 U.S.C. §112, first paragraph.

Claim 3 recites PDZ proteins that bind to E6 proteins from HPV strains 16, 18 and 45. The Examiner argues that this claim is unsupported by the specification because the specification assertedly does not describe binding of PDZ proteins to the E6 protein from HPV strain 45.

As noted above and solely to expedite prosecution, claim 3 has been amended to recite an oncogenic E6 protein detection method that employs MAGI-1 PDZ domain 2.

In view the above in combination with the Examiner's comments on MAGI1 domain 2 appearing to bind to all oncogenic HPV proteins, the Applicants submit that this rejection has been adequately addressed and may be withdrawn.

Data demonstrating that MAGI-1 PDZ domain 2 can bind to the E6 protein of HPV strain 45 can be provided if the Examiner deems it necessary.

Claim rejections under 35 U.S.C. § 103

Claims 1, 4-8, 10-13 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Bleul, in further view of either Kiyono or Gardiol.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claims 1, 6 and 10 are amended to recite the subject matter of claim 2.

Since claim 2 is not included in this rejection and all claims now recite the subject matter of claim 2, this rejection may be withdrawn. Withdrawal of this rejection is respectfully requested.

Claims 1, 4-8, 10-13 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Bleul and Lee.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claims 1, 6 and 10 are amended to recite the subject matter of claim 2.

Since claim 2 is not included in this rejection and all claims now recite the subject matter of claim 2, this rejection may be withdrawn. Withdrawal of this rejection is respectfully requested.

Claims 1-13 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Glausinger and Bleul.

The primary reference in this rejection, Davis, is cited to provide a broad teaching of specific binding assays using capture agents (e.g., monoclonal antibodies) that are bound to a solid support. Davis makes no hint that oncogenic strains of HPV can even be detected, let alone that oncogenic HPV strains can be specifically detected using a PDZ protein.

Bleul's disclosure is concerned with identifying serum-reactive structures in the oncogenic E6 protein of HPV 18 that would be useful for the diagnosis of HPV 18. Bleul identifies three serum-reactive epitopes on HPV 18. Bleul postulates that those epitopes could be used to detect HPV 18 E6 protein in blood serum. Bleul, like Davis, makes no suggestion that oncogenic E6 proteins can be specifically detected using a PDZ protein. Further, Bleul's teachings are restricted to detecting only HPV 18 E6 protein, not all oncogenic HPV E6 proteins.

Finally, Glausinger is cited to show that oncogenic E6 proteins from HPV 16 and 18 can, under certain experimental conditions, bind to a fusion protein containing a near full-length HA-

tagged MAGI-1 fusion protein. Glausinger, like Bluel and Davis, makes no suggestion that MAGI-1 can be used to specifically detect oncogenic E6 proteins. Glausinger neither suggests that the E6/MAGI-1 interaction is specific enough nor stable enough to be effective in a biological assay. Further, Glausinger teaches away from the invention: the second ¶ of col. 1 of p. 5277 states that that MAGI-1 is *degraded* in the presence of oncogenic E6 protein.

The Applicants submit that the claims of the present application are patentable in view of the teachings of Davis, Bluel and Glausinger for three basic reasons:

First, the Applicants submit that there is no suggestion in any of the prior art references that a PDZ domain of MAGI1 could specifically bind to the E6 proteins from *all* known oncogenic strains of HPV, thereby allowing it to be a key component of a highly specific, sensitive and straightforward test for oncogenic strains of HPV. Glausinger discloses an interaction between an oncogenic E6 protein and MAGI1. However, Glausinger did not disclose that such an interaction could be the basis for an effective test for all strains of HPV. Further, Glausinger neither tested the specificity of the interaction, never tested the strength of the interaction, never considered that MAGI-1 may interact with other oncogenic proteins, and never tested for the interaction using a biological sample (e.g., a biopsy). In fact, since the amino acid sequences of the carboxy-terminus of the E6 proteins tested by Glausinger (i.e., the E6 proteins of HPV strains 16 and 18) differ from the amino acid sequences of the carboxy-terminus of the E6 proteins from most other oncogenic strains of HPV (e.g., as listed in Table 3 on page 85 of the instant application), one of skill in the art would reasonably expect that MAGI-1 would *not* specifically bind to the E6 proteins from *all* known oncogenic strains of HPV.

That a PDZ domain from MAGI1 specifically binds to all oncogenic E6 proteins, but not non-oncogenic E6 proteins, could not have been predicted from the cited prior art references. This is particularly true in view of the fact that the C-terminal PDZ domain-binding motif amino acid sequence of oncogenic E6 proteins can be completely different between different E6 proteins. With this in mind, the Applicants note that in Glausinger's introduction, Glausinger states that PDZ domains bind to specific sequences motifs located at the C-terminus of target proteins. In support of this statement, Glausinger references Lee et al (Proc. Natl. Acad. Sci. 1997 94: 667-6675; copy attached hereto as Exhibit A) to illustrate the C-terminal PDZ-binding

consensus sequence found in HPV E6 proteins. In Lee's Table 2, however, Lee points out in the footnote that E6 proteins from HPV strains 26, 34 and 53 (which are oncogenic) "do not encode the consensus C-terminal PDZ domain-binding motif", implying that those proteins do not contain a PDZ binding motif and would therefore be undetectable using a PDZ protein. Further, the Applicants note that HPV strains 16 and 33 (both of which are of high oncogenic potential) are not encompassed by the motif set forth at the top of Lee's Table 2 , implying that they, too, would be undetectable by a PDZ protein. The cited art, particularly Lee, teaches away from the present invention.

One of skill in the art, in view of Glausinger's and Lee's disclosures, would almost certainly think that such a test would be quite *ineffective*, since so many oncogenic E6 proteins do not contain a PDZ binding motif at their C-terminus.

In summary, none of the prior art references, taken together or in combination, suggests using a PDZ domain of MAGI1 as an effective test for oncogenic strains of HPV. The prior art does simply fails to suggest that the MAGI1 PDZ domain 2 is sufficiently specific and robust to be used in a diagnostic test for oncogenic strains of HPV.

The Applicants submit that this rejection may be withdrawn on this basis alone.

Second and as noted above, Glausinger states in the second ¶ of col. 1 of p. 5277 that MAGI-1 is degraded in the presence of oncogenic E6 protein.

Upon reading Glausinger's statement, one of skill in the art would think that that MAGI1 would be unsuitable for use in a test for oncogenic E6 proteins since the MAGI1 protein would be degraded in performing the test.

Accordingly, Glausinger's statement would lead one of skill in the art directly away from the claimed invention.

In other words and in addition to the discussion in the prior section of this response, one of skill in the art would not combine the references of Davis, Glausinger and Bleul to provide an oncogenic E6 protein detection assay that employs a PDZ domain form MAGI1 because Glausinger states that the Magi-1 protein is degraded by oncogenic E6 proteins. Glausinger teaches away from the invention.

Finally, the Applicants note that the claims recite a protein containing MAGI1 PDZ domain 2. Glausinger, on the other hand, used a protein (full length MAGI1) that had a total of *five* PDZ domains (see Glausinger's Fig. 1). Glausinger failed to recognize that it is the PDZ domain 2 of MAGI1 that interacts with oncogenic E6 proteins.

The use of MAGI1 PDZ domain 2 in an assay for detecting oncogenic E6 proteins is therefore not suggested by Glausinger, Davis or Bleul.

In view of the cited art, therefore, one of skill in the art would have no reason to employ the PDZ domain 2 of MAGI1 in an HPV detection method – this simply is not pointed out in Glausinger's disclosure, and is not pointed out in any of the other cited references.

One of skill in the art would therefore find no suggestion to practice what is being claimed: a method employing the PDZ domain 2 of Magi-1.

The Applicants respectfully submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

Claim 14 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Glausinger, Bleul and Kehmeier. The Office asserts that Davis's general teachings of methods of analyte detection, in combination Bleul's HPV diagnostic assays, Glausinger's Magi-1–related results and Kehmeier's proteasome inhibitor, render the claims obvious.

As discussed above, Davis, Glausinger and Bleul are deficient for failing to suggest any method employing PDZ domain 2 of Magi-1 in a test for oncogenic E6 proteins. In fact, Glausinger's disclosure teaches away from such a method.

Kehmeier's proteasome inhibitor fails to meet the deficiency of Davis, Glausinger and Bleul, and, as such, the references cited in this rejection, taken in any combination, cannot render the current claims obvious under current law.

Withdrawal of this rejection is respectfully requested.

Double patenting

Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of claims of co-pending patent application 10/847,818.

Without any intention to acquiesce to the correctness of this provisional rejection, claims 1, 6 and 10 are amended to recite the subject matter of claim 2. The claims are now directed to methods that employ the PDZ domain 2 of MAGI-1.

The Applicants note that according to MPEP § 804, double patenting analysis should consider the *claims* of a first patent application in relation to the *claims* (rather than the entire specification) of a second application or patent. In other words, in attempting to establish a double-patenting rejection, the Office should restrict its analysis to the claims (and not the entire specification) of a cited patent or patent application. Further, according to MPEP § 804, any double patenting analysis should parallel the guidelines for analysis of obviousness under 35 U.S.C. § 103.

The Applicants submit that the instant claims are patentably distinct from the claims of 10/847,818 because the instant claims recite MAGI-1 domain 2, E6 and HPV. These elements are simply not present in and are not reasonably suggested by the claims of 10/847,818.

The Office's position that the claims of 10/847,818 are generic to the instant claims should have not bearing on the patentability of the instant claims since it is well established that an undisclosed species can be patentable over a genus that encompasses but does not describe that species.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number VITA-008.

Respectfully submitted,
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Date: July 18, 2005

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